Election/Restriction Requirement

The Office Action states that the claims 1-21 will be examined to the extent that they describe a protease variant modified by substitution and conjugation at a position that corresponds to any one position 17, 52, 89, 134, 155, and 265. Applicants hereby affirm the restriction requirement. Applicants will cancel the non-elected claims upon indication of allowance.

The Rejection under 35 U.S.C. 112, second paragraph

Claims 1-21 have been rejected under 35 U.S.C. 112, second paragraph as being indefinite. Specifically, claim 1 has been rejected because it does not recite the sequence identifier for the amino acid sequence. In response, Applicants have amended claim 1 as suggested by the Office Action to include "set forth in SEQ ID NO:1." Accordingly, Applicants respectfully submit that the rejection under 35 U.S.C. 112, second paragraph has been overcome.

Claims 1, 6, 7, and 12 have been rejected under 35 U.S.C. 112, second paragraph as being indefinite in reciting "corresponding to subtilisin BPN'" at the close of their constituent clauses or at the end of the claim. In response, Applicants have amended claims 1, 6, 7, and 12 as suggested by the Office Action by deleting the phrase. Accordingly, Applicants respectfully submit that the rejection under 35 U.S.C. 112, second paragraph has been overcome.

Claims 5 and 11 have been rejected under 35 U.S.C. 112, second paragraph as being indefinite in reciting at the close of the claim "and variants thereof." In response, Applicants have amended claims 5 and 11 as suggested by the Office Action by deleting the phrase. Accordingly, Applicants respectfully submit that the rejection under 35 U.S.C. 112, second paragraph has been overcome.

Claim 19 has been rejected under 35 U.S.C. 112, second paragraph as being indefinite by not explaining the part or aspect of the supplementary moiety. In response, Applicants have amended claim 19 by providing an additional description of the supplementary moiety. Accordingly, Applicants respectfully submit that the rejection under 35 U.S.C. 112, second paragraph has been overcome.

The Rejection under 35 U.S.C. 103(a) over von der Osten and Braxton

Claims 1-6, 8, 9, and 20 have been rejected under 35 U.S.C. 103(a) as being unpatentable over von der Osten et al. (US 6,300,116) and Braxton et al. (US 5,766,897). Applicants respectfully traverse this rejection for two reasons. First, there is no motivation to combine the references, as required in MPEP 2143.01. Second, the combined references do not teach or suggest all of the claim limitations, as required in MPEP 2143.03. None of the references suggest a protease conjugate comprising a protease moiety and one or more addition moieties wherein the protease moiety comprises a first epitope region, a second epitope region, and a third epitope region, wherein each addition moiety is covalently attached to an epitope protection position of the protease moiety as required by Applicants' claim 1. Thus, the obviousness rejection given in the Office Action does not establish a *prima facie* case of obviousness. Therefore, Applicants contend that the claimed invention is unobvious and that the rejection should be withdrawn.

Von der Osten teaches subtilase variants having modifications in an amino residue in which the amino acid sequence further had been modified at one or more of the amino acid residues in the vicinity of the autoproteolytic site. Braxton teaches substitution of cysteines for native amino acids to then conjugate polymers, including polyethylene glycol [PEG] polymers, in order to mask epitopes that may be recognized by a mammalian immune defense system. Von der Osten teaches improved autoproteolytic stability in subtilisin 309 at position 132, but makes no suggestion that stability could be accomplished through conjugation of polymers as taught in Braxton. One skilled in the art would have no motivation to combine von der Osten's teaching of altering amino acids in subtilisin 309 with Braxton's teachings of masking a polypeptide from immune surveillance. Von der Osten teaches targeting specific positions in order to improve autoproteolytic stability. Braxton, however, teaches random cysteine substitutions at a polypeptide region in order to protect it from immune surveillance. One skilled in the art would not have been motivated to combine von der Osten's teaching of controlled modification in subtilisin 309 with Braxton's random substitutions in different proteins for the purpose of immune surveillance.

In addition, the Office Action does not establish a *prima facie* case since the combined references fail to teach an element of the claimed invention. Von der Osten and Braxton do not teach a protease conjugate comprising a protease moiety and one or more addition moieties *wherein each addition moiety is covalently attached to an amino acid of the*

protease moiety at an epitope protection position. None of the prior references teach or suggest a protease conjugate comprised of a protease moiety and an addition moiety attached at an epitope protection position. The epitope protection position of the present invention aids in having a decreased immunogenic response yet allows the protease to maintain their activity as an efficient and active protease. There is no hint in the prior references that signify consideration that steric protection of epitope protection positions may decrease immunogenicity of the protease.

Therefore, Applicants contend that a *prima facie* case of obviousness has not been established, and the claimed invention is not obvious in view of the cited references.

The Rejection under 35 U.S.C. 103(a) over von der Osten, Braxton, and Powell

Claim 21 has been rejected under 35 U.S.C. 103(a) as being unpatentable over Von der Osten et al. (US 6,300,116), Braxton et al. (US 5,766,897), and Powell et al. (US 6,060,546). Applicants respectfully traverse this rejection for two reasons. First, there is no motivation to combine the references, as required in MPEP 2143.01. Second, the combined references do not teach or suggest all of the claim limitations, as required in MPEP 2143.03.

There is no motivation to combine von der Osten, or Braxton with Powell. Powell only teaches the preparation of a personal care composition comprising subtilisin SP 544, while the other references specifically teach subtilisin modification and substitution. One skilled in the art would not be motivated to combine references teaching specific modifications or substitutions of specific regions of different subtilisins with Powell's general description of a personal care composition comprising subtilisin SP 544. Von der Osten specifically teaches altering amino acids in subtilisin 309 to inhibit proteolysis, and Braxton specifically teaches substitution of cysteine to then conjugate polymers. While Powell teaches that subtilisins can be used in personal care compositions, there would be no motivation to combine that broad and general teaching with references teaching inhibition of proteolysis or polymer conjugation.

In addition, the Office Action does not establish a *prima facie* case since the combined references fail to teach an element of the claimed invention. Von der Osten, Braxton, and Powell do not teach a protease conjugate comprising a protease moiety and one or more addition moieties *wherein each addition moiety is covalently attached to an epitope*

protection position of the protease moiety. None of the prior references teach or suggest a protease conjugate comprised of a protease moiety and an addition moiety attached at an epitope protection position. The epitope protection position of the present invention aids in having a decreased immunogenic response yet allows the protease to maintain their activity as an efficient and active protease. There is no hint in the prior references that signifies consideration that steric protection of epitope protection positions may decrease immunogenicity of the protease.

Therefore, Applicants contend that a *prima facie* case of obviousness has not been established, and the claimed invention is not obvious in view of the cited references.

Conclusion

Applicants have made an earnest effort to place their application in proper form and to distinguish the invention as now claimed from the applied references. WHEREFORE, Applicants respectfully request reconsideration of this application, entry of the amendments presented herein and allowance of Claims 1-21.

Respectfully submitted,
D.N. Rubingh et al.

By BMP

Brent M. Peebles
Attorney for Applicants
Registration No. 38,576
(513) 626-2404

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Customer No. 27752

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims:

1. A protease conjugate comprising a protease moiety and one or more addition moieties wherein the protease moiety comprises a first epitope region, a second epitope region, and a third epitope region, wherein each addition moiety is covalently attached to an epitope protection position of the protease moiety, wherein:

   (a) the epitope protection positions for the first epitope region are selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 12, 17, 36, 40, 41, 43, 44, 45, 67, 86, 87, 89, 206, 209, 210, 212, 213, 214, 215, and 216 of the amino acid sequence of subtilisin BPN' set forth in SEQ ID NO:1 ~~corresponding to subtilisin BPN'~~;

   (b) the epitope protection positions for the second epitope region are selected from the group consisting of 25, 26, 27, 46, 47, 48, 49, 50, 51, 52, 53, 54, 91, 99, 100, 101, 102, 127, 128, 129, 130, 131, 132, 133, 134, 136, 137, 138, 140, 141, 144, and 145 of the amino acid sequence of subtilisin BPN' set forth in SEQ ID NO:1 ~~corresponding to subtilisin BPN'~~; and

   (c) the epitope protection positions for the third epitope region are selected from the group consisting of 9, 10, 22, 23, 24, 62, 63, 143, 146, 154, 155, 156, 157, 172, 173, 187, 189, 195, 197, 203, 204, 253, 254, 256, 265, 267, 269, 271, 272, and 275 of the amino acid sequence of subtilisin BPN' set forth in SEQ ID NO:1 ~~corresponding to subtilisin BPN'~~.

5. A protease conjugate according to Claim 4 wherein the parent amino acid sequence is selected from the group consisting of subtilisin BPN', subtilisin Carlsberg, subtilisin DY, subtilisin 309, proteinase K, thermitase, Protease A, Protease B, Protease C, and Protease D~~, and variants thereof~~.

6. A protease conjugate according to Claim 5 wherein:

(a) the epitope protection positions for the first epitope region are selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 12, 17, 40, 41, 43, 67, 86, 87, 89, 206, 209, 214, and 215 ~~corresponding to subtilisin BPN'~~;

(b) the epitope protection positions for the second epitope region are selected from the group consisting of 27, 47, 48, 50, 52, 102, 127, 128, 130, 131, 132, 134, 138, and 141 ~~corresponding to subtilisin BPN'~~; and

(c) the epitope protection positions for the third epitope region are selected from the group consisting of 22, 23, 24, 143, 146, 155, 173, 189, 197, 203, 204, 253, 254, 265, and 275 ~~corresponding to subtilisin BPN'~~.

7. A protease conjugate according to Claim 6 wherein the epitope protection positions for the first epitope region are selected from the group consisting of 1, 2, 3, 4, 5, 17, 40, 41, 43, 67, 86, 87, 89, and 214 ~~corresponding to subtilisin BPN'~~.

11. A protease conjugate according to Claim 10 wherein the first polypeptide is selected from the group consisting of subtilisin BPN', subtilisin Carlsberg, subtilisin DY, subtilisin 309, proteinase K, thermitase, Protease A, Protease B, Protease C, and Protease D~~, and variants thereof~~.

12. A protease conjugate according to Claim 11 wherein the first polypeptide is covalently attached to the linking moiety or the protease moiety at a position of the first polypeptide selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 9, 10, 12, 17, 22, 23, 24, 25, 26, 27, 36, 40, 41, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 62, 63, 67, 86, 87, 89, 91, 99, 100, 101, 102, 127, 128, 129, 130, 131, 132, 133, 134, 136, 137, 138, 140, 141, 143, 144, 145, 146, 154, 155, 156, 157, 172, 173, 187, 189, 195, 197, 203, 204, 206, 209, 210, 212, 213, 214, 215, 216 253, 254, 256, 265, 267, 269, 271, 272, and 275 ~~corresponding to subtilisin BPN'~~.

19. A protease conjugate according to Claim 1 additionally comprising one or more supplementary moieties selected from the group consisting of small molecules, polypeptides, and polymers.